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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
JUEDES, AMY E	
ART UNIT	PAPER NUMBER
1644	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/789,807	TJOA ET AL.	
	Examiner	Art Unit	
	AMY E. JUEDES	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 February 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 3-29* is/are pending in the application.

4a) Of the above claim(s) *4-7,10-12,16 and 24-29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 3, 8-9, 13-15, and 17-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment and remarks, filed 2/5/10, are acknowledged.

Claims 1 and 3-29 are pending.

Claims 4-7, 10-12, 16, and 24-29 stand withdrawn from further consideration pursuant to 37 CFR 1.14209 as being drawn to a nonelected inventions, there being no allowable generic or linking claim.

Claims 1, 3, 8-9, 13-15, and 17-23 are under examination.

2. Upon reconsideration, the rejection of the claims under 35 U.S.C. 103 is withdrawn.

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. Claims 1, 13-14, and 17-18 stand rejected under 35 U.S.C. 102(b) as being anticipated Matera et al., 2000.

As set forth previously, Matera et al. teach a method of differentiating dendritic cells comprising providing a population of peripheral blood monocytes that have been selected by magnetic sorting (i.e. "non-activated" as disclosed on page 10 of the instant specification), and contacting said monocytes with GM-CSF in the absence of additional cytokines (see page 30 and 31 in particular). Matera et al. also teach culturing in a serum free medium (see page 31 in particular). Matera et al. further teach that the dendritic cells generated by culture with GM-CSF express increased CD1a and decreased CD14 (see page 31 in particular). Additionally, the instant claims are drawn to a method of differentiating dendritic cells employing a dendritic cell precursor (i.e. a method of using a product made by a particular process). Thus, the method by which the monocytic precursor is produced does not carry patentable weight in the absence of a structurally difference (see MPEP 2113). The monocytic dendritic cell precursors of Matera et al. are the same as those produced by tangential flow filtration. Furthermore, the culture conditions comprising culture with GM-CSF taught by Matera et al. can be considered "non-activating" since they do not result in the progression of a fully mature dendritic cells (see page 35, in particular).

Applicant's arguments filed 2/5/10 have been fully considered, but they are not persuasive.

Applicant argues that although Matera et al. describe purifying CD14 positive cells with magnetic microbeads, the reference does not disclose any results specifically associated with these cells.

Matera et al. on page 30 teaches that the precursors can alternately be prepared by adherence or by positive selection of CD14 cells. Furthermore, the adherence protocol of Matera et al. is performed in the presence of 10% serum, which the instant specification discloses as a condition which prevents the tight adherence, and hence the activation, of monocytic cells (see page 22 of the instant specification, in particular).

Applicant further agues that Matera et al. teach that GM-CSF alone was found to be very effective at inducing macrophage like cells, and hence the method of Matera et al. does not result in the production of dendritic cells that are the same as those of the instant claims.

It is noted that the only structural requirements of the instant claims are that the cells express CD1a and have reduced CD14 expression, as taught by Matera et al. While Matera et al. do also characterize the cells as "macrophage-like" by morphological assessment; the cells express the same surface markers of the instant claims, which are markers characteristic of immature dendritic cells. Furthermore, the instant specification has not performed any morphological assessment to structurally define the cells of the instant claims, and the only structural features of the immature dendritic cells of the instant claims are the expression of the recited cell surface markers. Thus, the cells of Matera et al. are structurally identical to those of the instant claims irrespective of whether they also have some "macrophage-like" morphological characteristics.

Applicant further argues that the isolation method of Matera et al. can not be considered “non-activating”.

The term "non-activated" is not specifically defined in the specification. Thus, "non-activated" cells might encompass a wide range of conditions. For example, a monocyte that is treated under conditions under which proliferation is not induced might be considered "non-activated" (as is the case for both a CD14 positively selected cell and a cell selected by adherence, as taught by Matera et al.). Additionally, the instant specification specifically discloses on page 10 that antibodies can be used to positively select for non-activated monocyte like cells that express CD14. Thus, given the broadest reasonable interpretation of the instant claims, the precursors of Matera et al. can be considered "non-activated".

5. Claims 1, 14, and 17-18 are rejected under 35 U.S.C. 102(b) as being anticipated by Kasinrerk et al., 1993.

As set forth previously, Kasinrerk et al. teach a method of differentiating monocytes comprising providing a population of peripheral blood monocytes that have been selected by density centrifugation and negative selection (i.e. "non-activated"), and contacting said monocytes with GM-CSF in the absence of additional cytokines (see page 581 in particular). Kasinrerk et al. further teach that the resulting cells have increased expression of CD1a (see page 581 in particular). Kasinrerk et al. also teach that the resulting cells have decreased expression of CD14 (see page 581 in particular). Thus Kasinrerk et al. describe a cell identical to that of the instant claims (i.e. the cells are immature dendritic cells). Furthermore, the culture of the monocytes with GM-CSF alone in the absence of other stimulating cytokines, as taught by Kasinrerk et al. can be considered "non-activating" conditions, as recited in the instant claims. Additionally, the instant claims are drawn to a method of differentiation comprising providing a "monocytic" cell population (i.e. a method of using a product (a monocyte) made by a particular process). Thus, the method by which the monocytic precursor is produced does not carry patentable weight in the absence of a structurally difference (see MPEP 2113). Although the monocytes of Kasinrerk et al. have been purified using a different process than tangential flow filtration, they nevertheless are structurally the same as the monocytic precursor cells of the instant claims.

Applicant's arguments filed 2/5/10 have been fully considered, but they are not persuasive.

Applicant argues that the isolated monocytes were only tested for the expression of CD1a subsequent to culture with GM-CSF, and thus it is not possible to determine if the monocytes were "non-activated" after isolation.

Kasinrerk et al. teach that freshly isolated monocytes do not express CD1a (i.e. are "non-activated", see Fig. 1). Moreover, the instant specification on page 10 teaches that non-activated monocytes can be isolated by density centrifugation, and negative selection, which is exactly how the monocytes of Kasinrerk have been prepared. Thus, the monocytes of Kasinrerk are "non-activated".

Applicant further argues that there is not data provided regarding the presence of CD14.

Kasinrerk et al. teach on page 581, right column , that the isolated monocytes are CD14 positive, and that after culture in GM-CSF the cells demonstrate a decreased staining intensity for CD14 (i.e. have decreased CD14 expression).

6. The following are new grounds of rejection.

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3, 8-9, 13-15, and 17-23 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Specifically, the specification provides insufficient guidance to differentiate immature dendritic cells having CD1a and decreased expression of CD14, from non-activated monocytic precursors, as broadly claimed.

The specification disclosure is insufficient to enable one skilled in the art to practice the invention as claimed without an undue amount of experimentation. Undue experimentation must be considered in light of factors including: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary

skill in the art, the level of predictability of the art, the amount of direction provided by the inventor, the existence of working examples, and the quantity of experimentation needed to make or use the invention, see *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) states, "The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art." "The "amount of guidance or direction" refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling" (MPEP 2164.03). The MPEP further states that physiological activity can be considered inherently unpredictable. With these teachings in mind, an enabling disclosure, commensurate in scope with the breadth of the claimed invention, is required.

The instant claims are drawn to a method of differentiating monocytic precursors into immature dendritic cells having decreased expression of CD14 and increased expression of CD1a comprising contacting non-activated monocytic precursors with GM-CSF in the absence of additional cytokines. The state of the art is such that obtaining immature dendritic cells with GM-CSF in the absence of additional cytokines is extremely unpredictable. For example, Chaperot et al. teach a method identical to that of the instant claims, including culturing the monocyte precursors in non-adherent bags, but fail to obtain CD1a+ immature dendritic cells after culture in GM-CSF in the absence of additional cytokines. Chaperot et al. teach isolating the monocytic precursors by various methods including cytaphersis, density gradient preparation, and negative selection (see page 1668, in particular), which are conditions disclosed by the instant specification as "non-activating". Likewise, Bernard et al., 1998 (of record) teach a method identical to that of the instant claims, including culturing in PFTE bags,

but again fail to obtain immature dendritic cells with reduced CD14 expression by culture with GM-CSF in the absence of additional cytokines. Furthermore, Sallusto et al. (of record) culture monocytic precursors in the presence of a medium containing 10% serum along with GM-CSF alone, which as disclosed by the instant specification prevents tight adherence and activation of the cells. However, Sallusto et al. fail to obtain CD1a+ immature dendritic cells. While other references (i.e. Matera et al. and Kasinrerk al.) do obtain a population of CD1a+ cells displaying decreased expression of CD14 by culture in GM-CSF in the absence of additional cytokines, it is not readily apparent which factors are critical for successfully obtaining said cells compared to the methods of Sallusto et al, Bernard et al., or Chaperot et al. Thus, based on the extremely unpredictable nature of the art, the instant specification must provide a sufficient and enabling disclosure commensurate in scope with the instant claims.

The instant specification teaches that the critical factor in obtaining immature dendritic cells by culture with GM-CSF in the absence of additionally cytokines relates to the activation status of the monocytic precursors. The specification teaches that the monocytic precursors should be isolated and cultured in such a way as to prevent their activation. For example, the instant specification discloses that non-activated precursors can be obtained by inhibiting the tight adhesion of monocytic precursors to the culture surface. The specification discloses on page 6 that this can be accomplished by a using low avidity culture vessels, or by including a high concentration of animal serum in the culture. The instant specification further discloses various methods for isolating the monocytic precursors such that they are non-activated, but the disclosed methods are the same as those taught in the prior art, including aphaeresis, centrifugation, or positive/negative selection. The instant specification further provides specific examples in which monocytic precursors are cultured with GM-CSF in the absence of additional cytokines to obtain CD1a+ immature dendritic cells. The examples disclose culturing the cells in low-avidity bags, or with a high concentration of serum protein. However, both Bernard et al. and Chaperot et al. have performed the method using a low avidity culture vessel and isolation of the cells using a non-activating method, and failed to obtain CD1a+ immature dendritic cells with

reduced CD14 expression. Moreover, Sallusto et al. have cultured monocytic precursors with 10% serum, which according to the instant specification , should prevent tight adherence (and hence activation) of the precursors. However, Sallusto et al. also failed to obtain immature dendritic cells after culture in GM-CSF alone. Thus, it must be assumed that other critical factors are required to successfully perform the method of the instant claims, either in the cell isolation protocol or the cell culture conditions. Therefore, based on the unpredictability of the art, the instant specification does not provide sufficient guidance to enable one of skill in the art to obtain "non-activated" precursor as broadly claimed, that would result in a CD1a+ immature dendritic cell after culture with GM-CSF in the absence of additional cytokines.

8. No claim is allowed.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amy E. Juedes, whose telephone number is 571-272-4471. The examiner can normally be reached on 8am to 4:30pm, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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